REMARKS

With this amendment, Claims 51-52 and 74-105 are pending. Claims 53-73 have been cancelled without prejudice or disclaimer in Applicants' Amendment dated September 9, 2008. Claims 78-83 have been withdrawn by the Examiner as being drawn to non-elected species. Claims 51, 79, 80, 90, 93, 94, 95, 97, 98, 99, 104 and 105 are currently amended. New claim 106 has been added. Support for the amendments to claim 51 can be found throughout the specification as filed, such as at page 19, line 23. Support for the amendments to claims 51, 79, 80 and 99 can be found throughout the specification as filed, at least at page 3, line 2 and at page 42, lines 21-22. Support for the amendments to claim 90 can be found throughout the specification as filed, at least at page 21, lines 15-22. Support for the amendments to claims 93, 94 and 99 can be found throughout the specification as filed, at least at page 22, lines 9-10 and at page 25, line 30 - page 26, line 5. Support for the amendment to claim 95 can be found throughout the specification as filed, at least at page 26, line 21. Support for the amendments to claims 97 and 98 can be found throughout the specification as filed, for example, at least at page 25, line 34. Support for the amendment to claim 104 can be found throughout the specification as filed, at least at page 46, lines 23-24 and page 46, lines 27-28. Support for the amendment to claim 105 can be found throughout the specification as filed, at least at page 48, line 20 and page 48, line 28. Support for new claim 106 can be found in the specification as filed, for example at page 23, lines 3-4. No new matter has been added by way of the present amendments.

Amendments to the specification have been made to state the date of the deposit of the hybridoma cell line of accession number DSM ACC2542 and the complete address of the depository. No new matter has been added by way of the present amendments.

I. Amendment and Reply filed September 9, 2008

Applicants thank the Examiner for acknowledging the Amendment and Reply filed September 9, 2008.

II. Species election

Applicants thank the Examiner for acknowledging the election without traverse of a CD3/CD14 expressing cell as the species of transplant acceptance inducing cell in the Amendment and Reply filed on September 9, 2008. Upon the finding of allowable subject matter, Applicants reserve the right to consideration of claims to additional species. Applicants understand that Claim 51 is considered generic with respect to all species elections and is under consideration to the extent that it reads on the elected species. Claims 78-83 may be examined in this application should the elected species be found allowable.

III. Response to Rejections

A. Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 90-92, 95, 97-98 and 104-105 as allegedly being unpatentable under 35 U.S.C. § 112, first paragraph. The Examiner has stated that the specification allegedly does not contain a written description of the claimed invention. Applicants respectfully traverse this rejection.

1. Claims 90-92

Applicants thank the Examiner for stating that page 22 of the instant specification "discloses that the transplant inducing cell of the invention can be a part [of] a cell population comprising lymphocytes." Office Action at page 3. The Examiner further states that "the disclosure by the specification of culturing transplant [acceptance] inducing cells in vitro with lymphocytes to expand CD4+CD25+ regulatory T cells for administration to a subject has a narrower scope than the instant claims." *Id.* The Examiner then concludes that "the specification only discloses co-culturing a transplant-acceptance inducing cell with a lymphocyte to generate said administered regulatory T cells." Office Action at page 4. Applicants respectfully disagree with the Examiner's conclusion. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended

claim 90 to recite that said lymphocyte is co-cultivated with a self-tolerance inducing cell to induce formation of regulatory T lymphocytes such as CD4+/CD25+ lymphocytes.

The Examiner further alleges that "the disclosure by the specification of culturing transplant inducing cells in vitro with lymphocytes to expand CD4+CD25+ regulatory T cells for administration to a subject has a narrower scope than the instant claims." *See* Office Action at page 3. The Examiner concludes that "the specification only discloses co-culturing a transplant-acceptance inducing cell with a lymphocyte to generate said administered regulatory T cells." Office Action at page 4. Applicants respectfully disagree with the Examiner's contentions and conclusion. In Examples 7A and 7B (on pages 48 and 50, respectively, of the specification as filed), animals were injected with lymphocytes from a recipient animal that had been previously directly co-cultivated with transplant acceptance inducing cells. As such, the specification clearly discloses a method of administering a transplant-acceptance inducing cell composition comprising lymphocytes having CD4 and CD25 on their cell surface. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 90 (and therefore dependent claims 91 and 92) has been overcome and should be withdrawn.

2. Claims 97-98

The Examiner has alleged that the specification discloses that cell preparations comprising tolerance inducing cells can comprise about 10-50% of lymphocytes. From this, the Examiner concluded that "[t]he recitation [in the claims] of 'at least 10%' has no upper limit, and has a different scope than the range of 10-50% disclosed by the specification." Office Action at page 4. Applicants respectfully disagree with the Examiner's conclusion. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claims 97-98 to recite that lymphocytes comprise from about 10% to 50% of the total population of cells. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 97-98 has been rendered moot and should be withdrawn.

3. Claim 95

The Examiner has stated that the specification discloses culturing monocytes with 2 to 20 μg/L of M-CSF, but that the instant claims recite that the concentration of M-CSF is 1 to 20 μg/ml. Applicants thank the Examiner for pointing this out, and have amended claim 95 to recite that the M-CSF in the culture medium is 1 to 20 μg/L. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 95 has been rendered moot and should be withdrawn.

4. Claim 104

The Examiner has alleged that the specification "discloses specific examples in which the cells are administered 7 days prior to transplantation, or 7 days and 1 day prior to transplantation." Office Action at page 4. The Examiner concludes that the disclosure of the specification "has a different scope than the instant claims which recite that the cells are administered 'up to 7 days' prior to transplantation." Office Action at page 4. Applicants respectfully disagree with the Examiner's conclusions. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claim 104 to recite that said transplant-acceptance inducing cell is administered to said subject 1 day or 7 days prior to said transplantation of said organ. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 104 has been rendered moot and should be withdrawn.

5. Claim 105

The Examiner has alleged that "the specification discloses that in the case of post-transplant cell administration, the period between transplant and the single administration of the cells should not be longer than 7 days." Office Action at page 5. The Examiner concludes that "the specification does not provide adequate support for a method of administering cells 'up to 10 days' following transplantation, as recited in the instant claims." Office Action at page 5. Applicants respectfully disagree with the Examiner's conclusions. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claim 105 to recite that said transplant-acceptance inducing cell is administered to said

subject 7 days or 10 days following said transplantation of said organ. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 105 has been rendered moot and should be withdrawn.

B. Rejection under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 76-77 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. The Examiner has stated that claims 76-77 allegedly do not comply with the enablement requirement because the "claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art... to make and/or use the invention." Further, the Examiner alleges that the "GM-7" hybridoma cell line is required to practice the current invention. Office Action at page 5. It is not. No antibody is required to practice the method of claims 76-77. The Examiner states that the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines. Applicants respectfully submit that even if the cell line recited in claims 76-77 was required, the cell line was deposited according to the Budapest Treaty. Applicants have amended the instant specification to include the complete name and address of the depository as well as the date of deposit of the cell line. The recited cell line was deposited on May 13, 2002. Applicants respectfully submit that the Examiner's rejection of claims 76-77 has been overcome and should be withdrawn.

Claims 51-52, 74-77 and 84-105 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

Applicants thank the Examiner for indicating that the specification is enabling for

> a method for the suppression of transplant rejection reactions to a donor transplant in a subject comprising administering a CD3+CD14+ transplant acceptance-inducing cell of donor origin to said subject, wherein the cell is obtained by a process comprising isolating a blood cell population comprising monocytes and lymphocytes from the donor, multiplying said cell population with M-CSF, followed by cultivating said cell population with γ-IFN, and a method for the suppression of transplant rejection reactions to a donor transplant in a subject comprising administering a transplant acceptance-inducing cell of donor origin to

> said subject, wherein the cell is obtained by a process comprising isolating a blood cell population comprising monocytes and lymphocytes from the donor, multiplying said cell population with M-CSF, followed by cultivating said cell population with γ-IFN.

Office Action at page 6. The Examiner alleges that "[t]he instant claims do not require that the transplant acceptance inducing cell be derived from the donor of the transplant... However, the instant specification on page 42 demonstrates that suppression of transplant rejection requires the administration of cells from the donor of the transplanted tissue, since no suppression is seen when cells of a third party donor are administered." Office Action at pages 7-8. The Examiner concludes that "the method of the claims only functions to suppress a donor transplant rejection in a subject after administration of a transplant acceptance-inducing cell from said donor." Office Action at page 8. Applicants respectfully disagree with the Examiner's contentions and conclusions. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claims 51, 79, 80 and 99 to recite that the transplant acceptance-inducing cell is derived from a donor. Therefore, Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been rendered moot and should be withdrawn.

In the Office Action at page 8, the Examiner speculates that "it appears likely that the CD3 'expressing' monocytes described by the instant specification are in fact CD3+ monocytes that have acquired CD3/TCR complexes by co-culture with T cells. In fact, the instant specification demonstrates in Example 11 that the expression of CD3 by the monocytic transplantation acceptance inducing cells requires the presence of lymphocytes." The Examiner then concludes that "CD3+CD14+ cells might be generated using other cytokine combinations by co-culture with lymphocytes." Office Action at page 9.

Applicants respectfully disagree with the Examiner's conclusion and draw the Examiner's attention to Example 10 of the specification as filed, which discloses cultivation of cell cultures containing only monocytes ("Mo") and cell cultures containing monocytes and lymphocytes ("Mo+Ly"). Moreover, the specification states that "[d]uring the cultivation, CD14+/CD3+ cells effective as TAIC [transplant acceptance inducing cells] are formed in both cultures." *See* specification as filed at page 58, lines 11-12. However, solely in order to advance

prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claims 93, 94, 97, 98 and 99 to recite that lymphocytes and granulocytes comprise from about 10% to about 50% of the total population of cells. Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

The Examiner has alleged that "the generation of monocytes . . . capable of suppressing an immune response is unpredictable and highly dependent on the cell culture conditions employed." The Examiner states that γ-IFN can suppress T cells *in vitro* if it is added simultaneously with M-CSF, but that it does not abrogate the suppressive effect of the monocytic cells if it is added after the M-CSF cultures have already been established. *See* Office Action at page 9. Applicants disagree but, solely to facilitate prosecution, have amended claims 93, 94 and 99 to recite that monocytes are cultivated with γ-IFN after they are cultivated with M-CSF. Therefore, Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

In the Office Action at page 10, the Examiner alleges that "[t]he specification does not demonstrate that these [CD3+CD14+] cells are responsible for suppressing transplant rejection in vivo, nor does the specification provide evidence that any CD3+CD14+ cell (for example, those derived by transfer of CD3 onto monocytes in a co-culture with T cells in the absence of M-CSF/γ-IFN) are capable of suppressing transplant rejection." The Examiner concludes that "the teachings of the specification are not commensurate in scope with the instant claims, which encompass suppressing transplant rejection with any CD14 and CD3 expressing cell...." While not arguing with the conclusions drawn, as discussed above, the present claims have been amended to recite that monocytes and lymphocytes are co-cultivated in culture medium containing M-CSF, followed by cultivation in culture medium containing γ-IFN. Therefore, Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

In the Office Action at page 10, the Examiner alleges that "example 11 of the specification demonstrates that the CD3+ cells are only obtained when monocytes and lymphocytes are co-cultured." The Examiner also alleges that "claim 99, which is not limited to administering a CD3+ cell, also recites that isolated monocytes are cultured to induce a

transplant acceptance inducing cell." The Examiner then concludes that "the specification is not enabling for a method of suppressing transplant rejection by administering an isolated monocyte cultured with M-CSF/γ-IFN, since all of the examples demonstrate the requirement of lymphocytes along with the monocytes to generate suppressive cells." Applicants respectfully disagree. As discussed above, Example 10 of the specification as filed discloses cultivation of cell cultures containing only monocytes ("Mo") and containing monocytes and lymphocytes ("Mo+Ly"). The specification also clearly states that "[d]uring the cultivation, CD14+/CD3+ cells effective as TAIC [transplant acceptance inducing cells] are formed in both cultures." *See* specification as filed at page 58, lines 11-12. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claims 93, 94, 97, 98 and 99 to recite that lymphocytes and granulocytes comprise from about 10% to about 50% of the total population of cells. Therefore, for at least the reasons stated above, Applicants respectfully submit that the Examiner's rejection of claims 51-52, 74-77 and 84-105 under 35 U.S.C. § 112, first paragraph has been overcome and should be withdrawn.

C. Provisional Rejection on the Ground of Nonstatutory Non-Obviousness Type Double Patenting

The Examiner has provisionally rejected Claims 51-52, 74-77 and 84-105 as allegedly being unpatentable over claims 54, 73, 78-81, 88-90 and 92-99 of copending Application No. 10/563,956 ("the '956 application") in view of WO 02/056830. The Examiner asserts that "it would have been obvious to treat transplantation rejection as the disease associated with disturbed self tolerance in the method claimed in the '956 application, since WO 02/056830 teaches that monocyte derived cells capable of inducing tolerance are useful for treating both autoimmune disease and transplantation rejection." *See* Office Action at page 12. Applicants respectfully disagree. Transplant acceptance inducing cells are allogeneic to the patient to be treated, while self tolerance inducing cells are autologous in this respect. However, in order to facilitate prosecution, Applicants are willing to consider submitting a terminal disclaimer in the present case with regard to Application No. 10/563,956 upon an indication of allowable subject matter. As such, Applicants respectfully request that this rejection of claims 51-52, 74-77 and

84-105 be held in abeyance until the Examiner provides an indication of allowable subject matter. Additionally, it is noted that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *See, e.g., Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991) ("filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection.").

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objections and rejections and pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-6237 should any additional information be necessary for allowance.

Respectfully submitted,

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